

# **Exhibit 12**

UNITED STATES DISTRICT COURT  
SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen – ASD-ADHD  
Products Liability Litigation

22:md-3043 (DLC)

This Document Relates To: All Actions

**RULE 26 EXPERT REPORT SUPPLEMENT OF ROBERT M. CABRERA, Ph.D.**

My name is Robert M. Cabrera, Ph.D. and this shall serve as my Rule 26 Expert Report Supplement for the above-referenced matter pursuant to Federal Rule of Civil Procedure 26(e)(2).

A recent study by Klein et al. (2023)<sup>1</sup> supports that *in utero* APAP (350mg/kg/day) exposure from post-implantation (GD6) to term interacts with the endocannabinoid system and causes core behaviors of neurodevelopmental disorders in Wistar rats. A total of 56 litters were exposed to APAP compared to offspring from 48 control litters exposed to vehicle (water). Consistent with this report and the growing body of evidence supporting APAP causing neurodevelopmental toxicity and disorders, the authors state that,

Meta-analyses of the epidemiological studies reported gestational exposure to PAR as a risk factor for autism spectrum disorders (ASD) (Alemany et al., 2021; Masarwa et al., 2018) and attention-deficit hyperactivity disorder (ADHD) symptoms (Alemany et al., 2021; Gou et al., 2019; Masarwa et al., 2018) in the progeny.

The term “risk factor” was coined from research done in the Framingham Heart Study, that reported increased levels of cholesterol or elevated blood pressure increased risk for coronary heart disease.<sup>2</sup> Klein et al. (2023) reported no significant changes in dam or pup weights, which is generally used to monitor alterations in feeding as a measure of overt toxicity. The behavioral testing performed included nest-seeking (olfactory), open field (motor activity and anxiety behavior), apomorphine challenge (stereotyped behavior), marble burying (repetitive behavior), and the three-chamber test (sociability). Comparisons included APAP exposure versus controls, each with an arm with and without a low dose WIN 55,212–2 (WIN, 0.3 mg/kg) exposure. WIN is a non-specific cannabinoid receptor agonist, so this arm was done to examine APAP-cannabinoid interactions. Results indicated 113 litters were included in the study, but nine were excluded because of smaller litter sizes (<8 pups), resulting in 104 litters with 8-16 pups. There were no statistically significant differences in general toxicity, with the average litter being  $12.71 \pm 1.56$  and  $12.18 \pm 1.64$ , in controls versus APAP treated, respectively ( $p=0.096$ ). There were also no statistically significant differences in maternal or pup weights in relation to APAP treatment. Nest

<sup>1</sup> Klein et al. Gestational paracetamol exposure induces core behaviors of neurodevelopmental disorders in infant rats and modifies response to a cannabinoid agonist in females. *Neurotoxicol Teratol.* 2023 Jun 28:107279. doi: 10.1016/j.ntt.2023.107279. Epub ahead of print. PMID: 37391024.

<sup>2</sup> Kannel et al. Factors of risk in the development of coronary heart disease--six-year follow-up experience. The Framingham Study. *Ann Intern Med.* 1961 Jul;55:33-50. doi: 10.7326/0003-4819-55-1-33. PMID: 13751193.

seeking results identified a significant interaction with APAP and WIN. Specifically, APAP exposure increased latency to reach nest bedding. WIN reversed these response profiles, reducing latency in APAP-exposed females and increasing latency in the control group. In open field, APAP exposure increased activity independent of sex and increased time in central area specifically in females. These data are consistent with increased activity (hyperactivity) with decreased anxiety in females; males did have a lower average time in the central areas (increased anxiety), but differences in males were not statistically different. Female offspring exposed gestationally to APAP also showed increased stereotyped behavior with apomorphine challenge, but this result was not found in male offspring. In the marble burying test, there was increased burying (repetitive behaviors) due to gestational APAP exposure, with males also burying fewer marbles than females. The authors also describe the utility of marble burying and the debates pertaining to the measure of anxiety versus repetitive behaviors by this test,

In the anxiety perspective, the higher the number of marbles buried, the higher the anxiety. For the compulsive perspective, increased burying indicates increased repetitive digging. Considering PAR-exposed females spent more time in the central area of the open field, which is indicative of a decreased anxiety state (Prut and Belzung, 2003),<sup>3</sup> altered emotionality is less likely to explain the result observed in marble burying test.

In these and other APAP experiments, the increased marble burying is thereby supported as a function of repetitive behavior and has been presented accordingly. The authors report no effects of exposure, sex, or WIN in the three-chamber test.

The authors conclude,

Summing up, our study demonstrates altered response to a CB1/CB2 agonist, enhanced induced-stereotypy and reduced anxiety state in females but not males gestationally exposed to PAR. Exposed males and females presented hyperactivity and increased repetitive behavior. Observed behavioral alterations are similar to some of the core symptoms of ASD (stereotyped/repetitive behaviors) and ADHD (hyperactivity), and this may suggest a role for gestational PAR exposure in increasing risk for these neurodevelopmental disorders.

Limitations of the study included using only a single dose. Analysis for the dose response requires the use of multiple dosages, which are not available in this study. The study identified sex-based differences but did not identify the mechanisms by which APAP exposure differentially impacted male and female rats, such as hormonal, genetic, or epigenetic factors.

Regarding the suggested reproductive, developmental, and neurodevelopmental impact of cannabinoids and modifying the endocannabinoid system, this impact has previously been reviewed in a three-part series (2022).<sup>4</sup> This series includes an adverse outcome pathway consistent

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<sup>3</sup> Prut and Belzung. The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: a review. *European Journal of Pharmacology*. 2003. 463: 1–3, 3-33. doi.org/10.1016/S0014-2999(03)01272-X

<sup>4</sup> Campbell et al. Animal evidence considered in determination of cannabis smoke and  $\Delta^9$ -tetrahydrocannabinol as causing reproductive toxicity (developmental endpoint); Part I. Somatic development. *Birth Defects Res.* 2022 Nov 1;114(18):1143-1154. doi: 10.1002/bdr2.2099. Epub 2022 Sep 30. PMID: 36177831.; Iyer et al. Animal evidence

with this report and provide additional support for the developmental toxicity of APAP and interaction of APAP with the developing nervous system and endocannabinoid system through multiple mechanisms.

In summary, APAP had damaging impacts on neurodevelopment in this study, consistent with ASD and ADHD behaviors. This study is considered “some evidence of developmental toxicity.”<sup>5</sup>

I expressly reserve the right to amend or supplement this supplemental report and to read, review and comment upon any reports prepared by Defendants’ experts.

All opinions offered herein are held to a reasonable degree of scientific certainty and are incorporated by reference into my Amended Expert Report served on June 22, 2023.

Dated: July 17, 2023

Respectfully submitted,



Robert M. Cabrera, Ph.D.

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considered in determination of cannabis smoke and  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) as causing reproductive toxicity (developmental endpoint); Part II. Neurodevelopmental effects. Birth Defects Res. 2022 Nov 1;114(18):1155-1168. doi: 10.1002/bdr2.2084. Epub 2022 Sep 16. PMID: 36111653.; Niknam et al. Animal evidence considered in determination of cannabis smoke and  $\Delta^9$ -tetrahydrocannabinol as causing reproductive toxicity (developmental endpoint); Part III. Proposed neurodevelopmental mechanisms of action. Birth Defects Res. 2022 Nov 1;114(18):1169-1185. doi: 10.1002/bdr2.2088. Epub 2022 Sep 20. PMID: 36125082.

<sup>5</sup> NTP- Explanation of Levels of Evidence for Developmental Toxicity. <http://ntp.niehs.nih.gov/go/10003>. Paul M. Foster.